DSI and Bioresearch Monitoring (BIMO)

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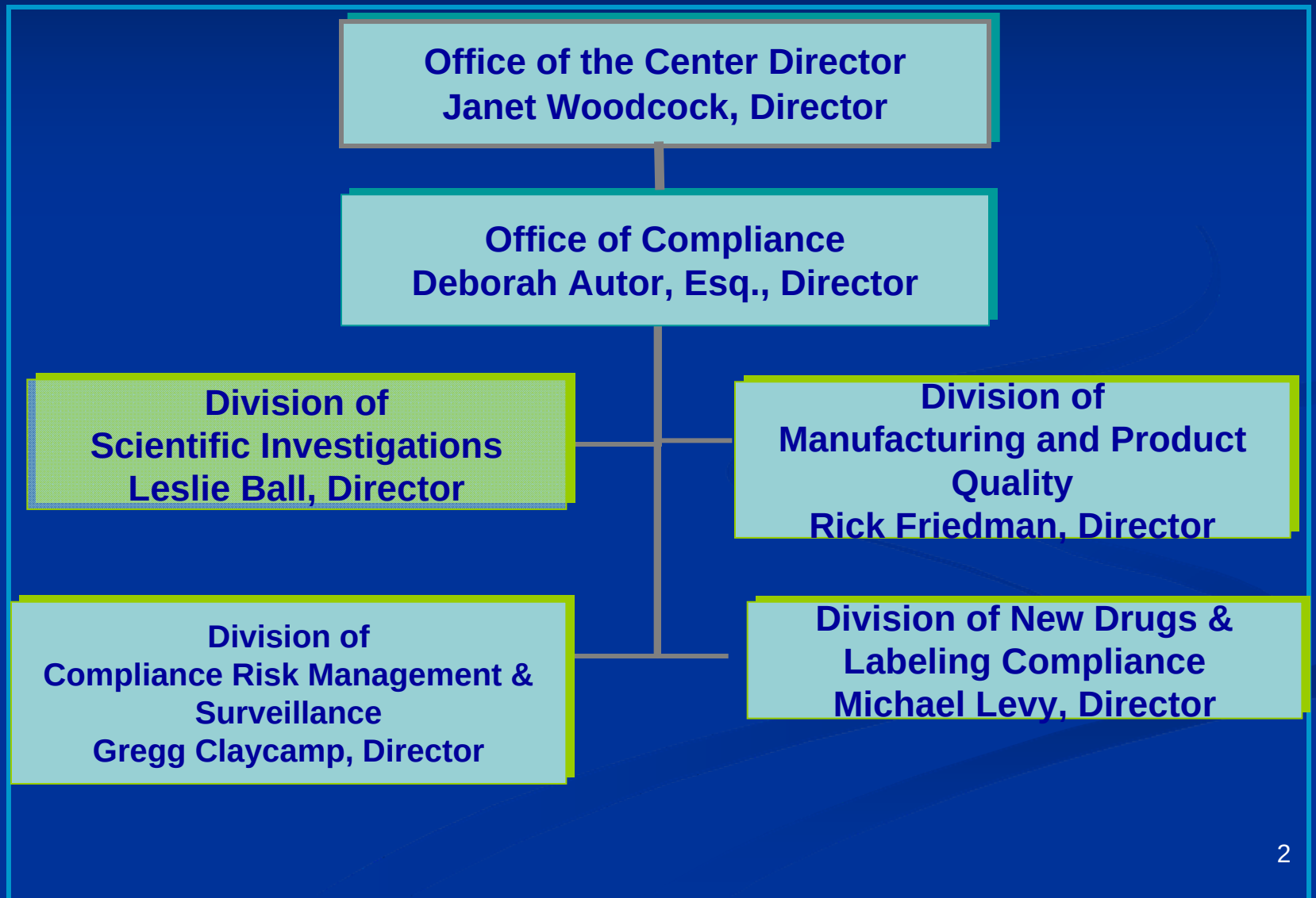
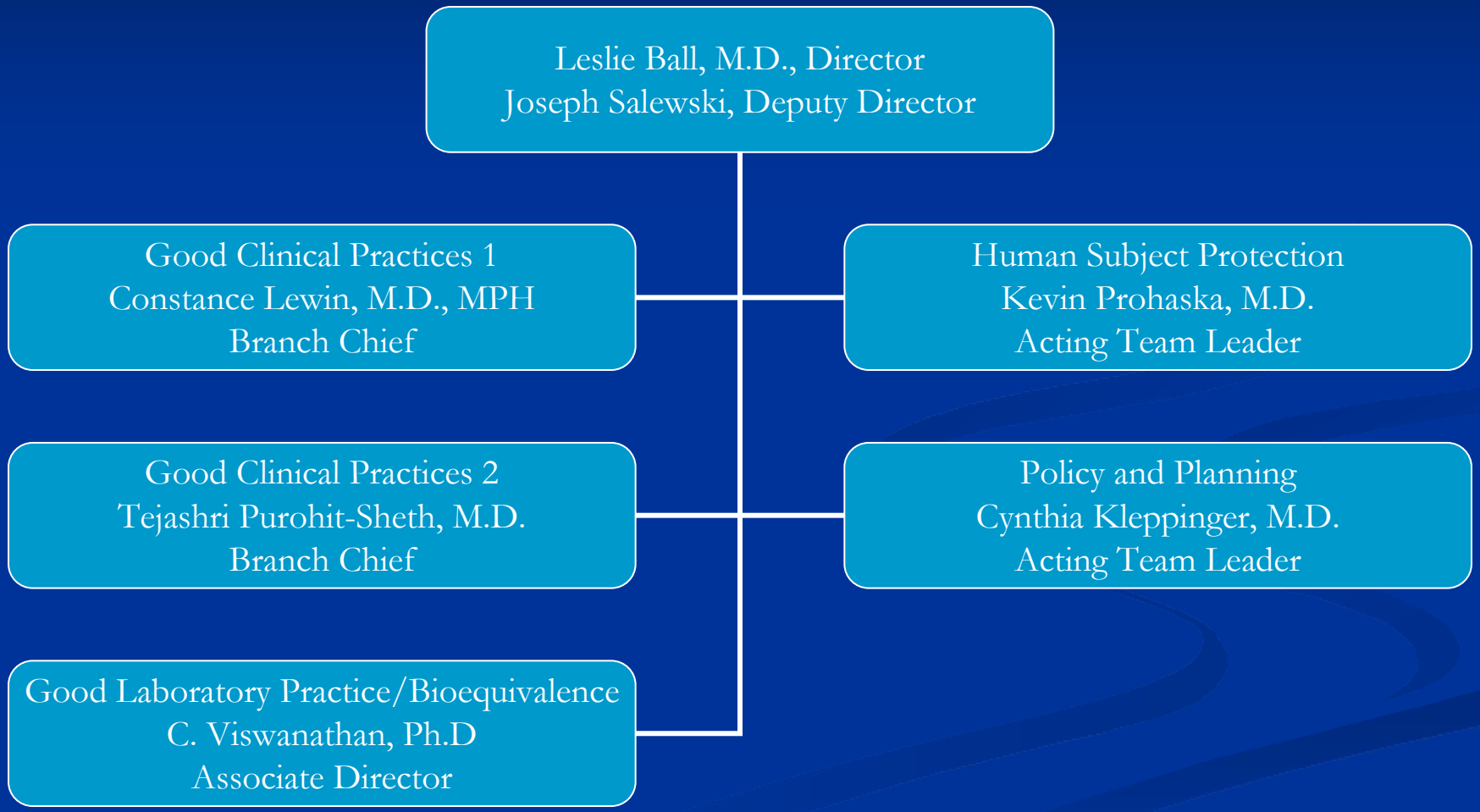
Center for Drug Evaluation and Research



Division of Scientific Investigation



GCP Staff Organization

- Two branches are organized by function
  - GCP-1: Complaints, Warning Letters
  - GCP-2: PDUFA-related inspections
- Reviewers are assigned to OND Review Divsions

Note: Please route Consults (inspection requests) through the Branch Chiefs/Team Leaders

- Complaints: Dr. Constance Lewin, GCP-1
- PDUFA-related: Dr. Tejashri Purohit-Sheth, GCP-2
- Human Subject Protection: Dr. Kevin Prohaska, HSP

Overview of BIMO

FDA's BIMO Program

- FDA's Bioresearch Monitoring Program - A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

Program Objectives

- To verify the quality and integrity of research data
- To protect the rights and welfare of human research subjects
- To ensure that FDA regulated research is conducted in compliance with applicable regulations

What we do in CDER/DSI/GCP

- **For the Review Divisions**
  - DSI will arrange for routine data audit GCP inspections to determine data integrity and safety of subjects in pivotal clinical trials, and provide the inspection reports to the review division prior to the Division Action Goal Date (GCP-1)
- **For the Public**
  - DSI will investigate complaints related to the conduct of clinical trials, including arranging for directed or "for cause" inspections, and take appropriate regulatory action (GCP-2)
  - DSI will arrange for routine surveillance inspections of IRBs to determine if rights, safety, and welfare of human subjects are protected (HSP)

How does DSI implement BIMO?

- Consulting service to Review Divisions
- Assigns and Performs inspections through the Office of Regulatory Affairs (ORA)
  - to verify data submitted in support of New Drug Applications (NDAs)
  - Investigates allegations of regulatory non-compliance
- Provides a scientific and medical review of Establishment Inspection Reports (EIRs) generated by ORA
- Makes recommendations regarding data to Review Divisions and directs regulatory actions

CDER's BIMO Program Responsibilities

- Ensure adherence to applicable regulations with respect to:
  - Good Laboratory Practice (GLP)
    - *In vivo* Bioequivalence
  - Good Clinical Practice (GCP)
    - Institutional Review Boards
    - Clinical Investigators
    - Sponsor-Monitors, CROs

CDER GCP Regulations

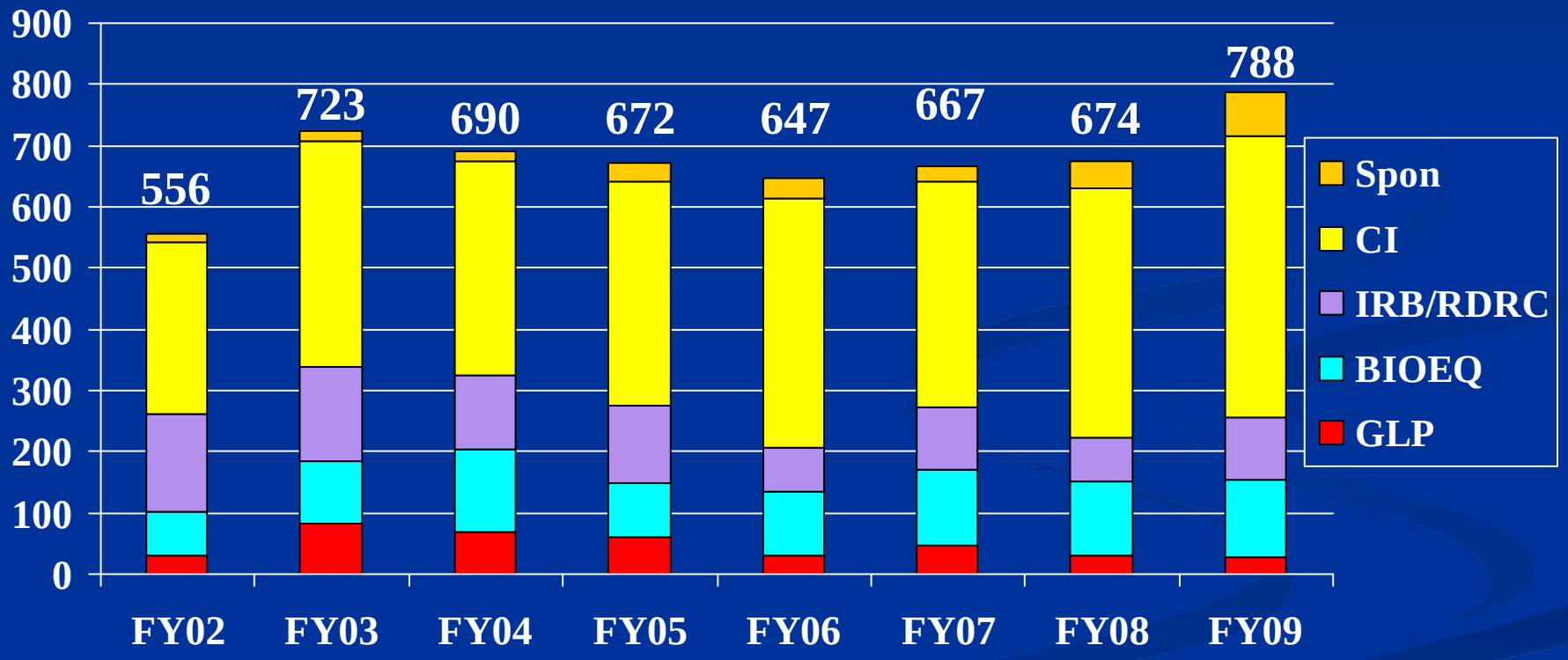
Applies to:	Clinical research involving products regulated by FDA
Regulatory oversight	IRBs, Sponsors, CROs, Monitors, Clinical Investigators
Relevant CFRs include (but not limited to…)	21 CFR 50, 54, 56 ▪Part 50: Protection of Human Subjects ▪Part 54: Financial Disclosure ▪Part 56: IRBs 21 CFR 312 (IND) 21 CFR 314 (NDA)
Penalties for non-compliance include (but not limited to…)	IRBs: (Administrative actions, Disqualification) Sponsors: Rejection of data; Clinical Holds; Termination of IND; Application Integrity Policy CI: Warning Letters, Disqualification (312.70), Debarment

BIMO Inspections

BIMO Inspections

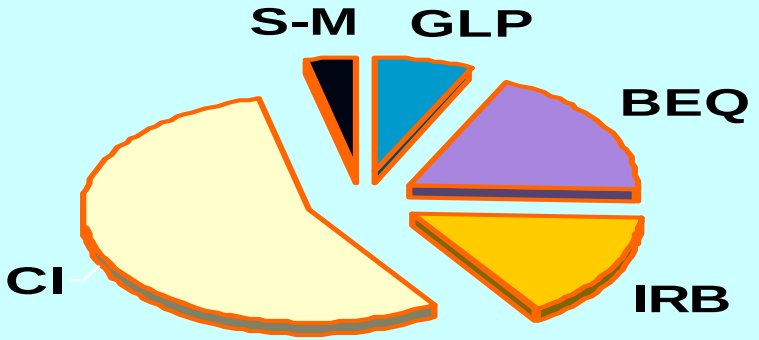
- Each FDA Center (CDER, CBER, CDRH, etc.) has oversight of inspections of research related to the product (s) it regulates
- Inspections are usually conducted by Office of Regulatory Affairs (ORA) field investigators
  - Field inspectors are NOT specifically assigned to CDER
  - All Field inspectors are responsible for conducting inspections for all centers (CBER, CDER, CDRH, CFSAN, etc.)
- Center personnel may participate

CDER BIMO Inspections*
FY 2002-2009**



*Based on inspection start date
**FY09 to Date

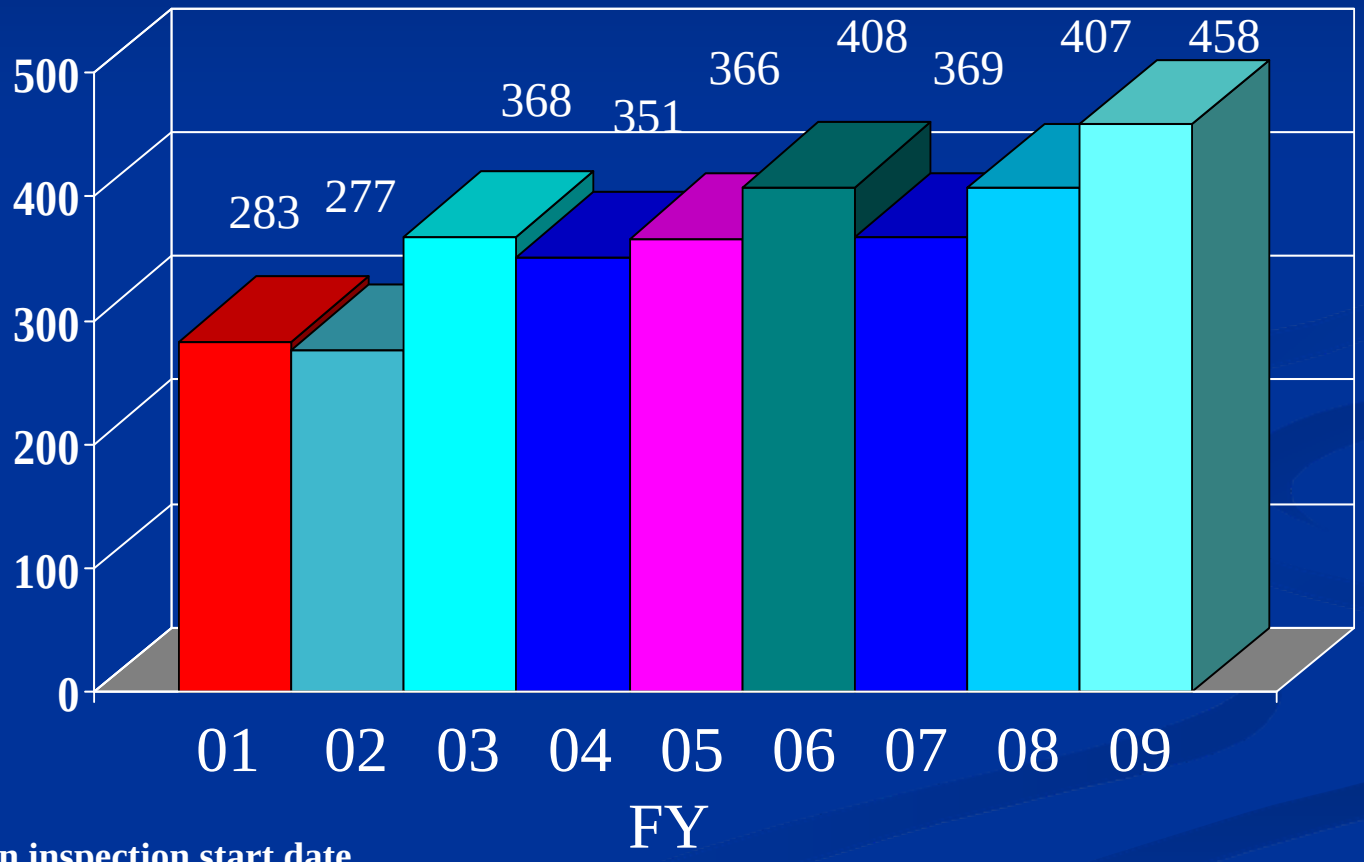
CDER BIMO Inspections*(FY 2009**)



CI = 458
BEQ = 128
IRB = 102
GLP = 27
S/M = 73
Total = 788

*Based on Inspection Start Date
**FY09 to Date

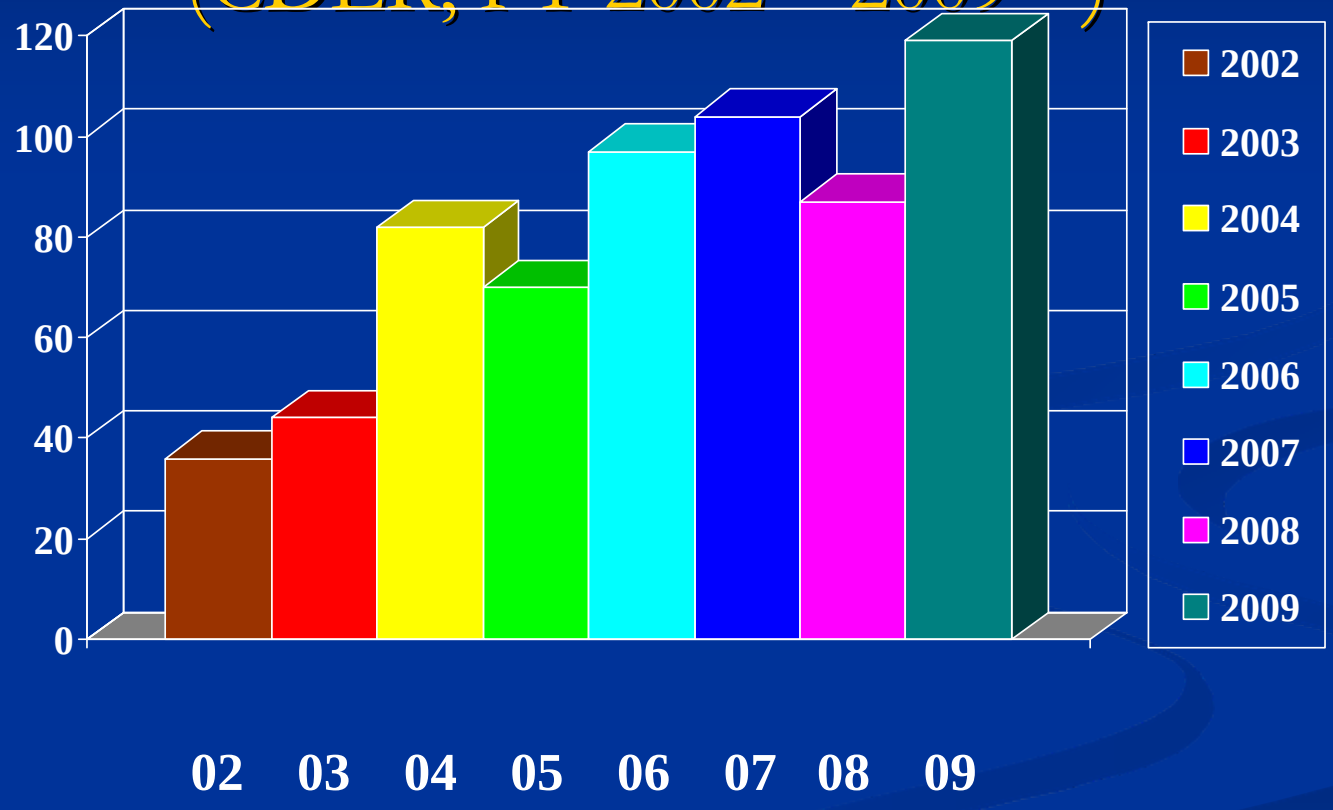
Clinical Investigator Inspections* CDER FY 2001-2009**



*Based on inspection start date

**FY09 to Date

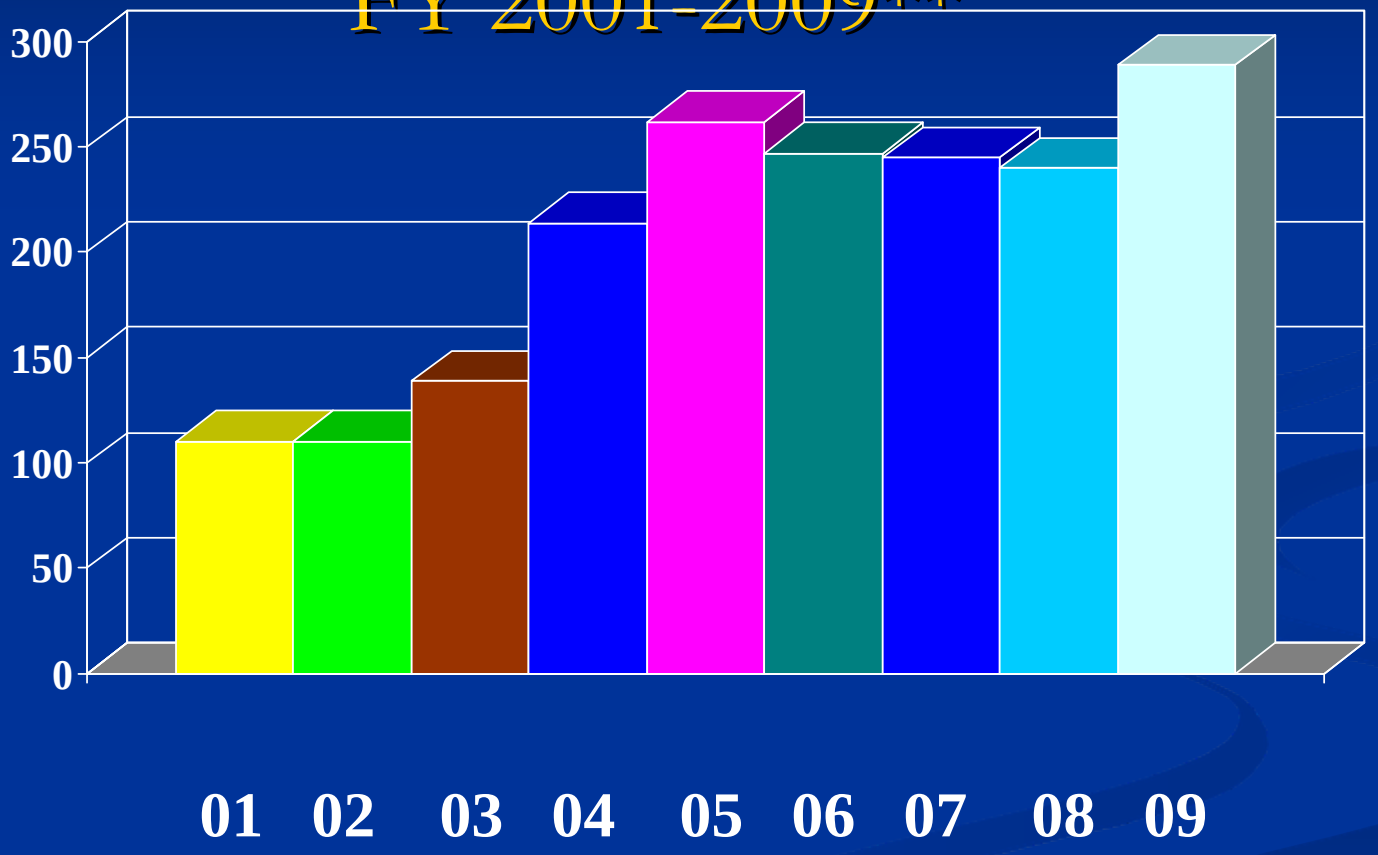
Clinical Investigator Inspections –International* (CDER, FY 2002 – 2009**)



N=119

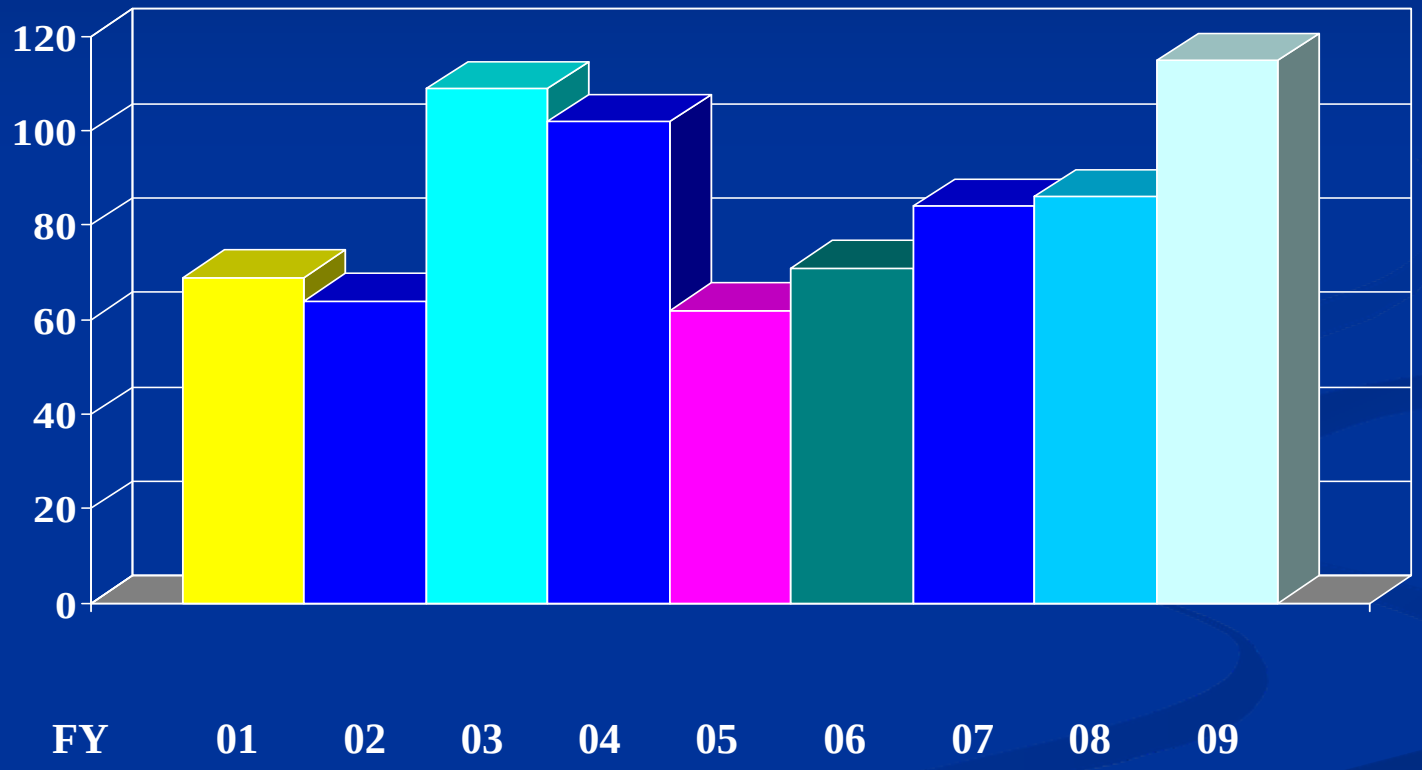
*Based on Inspection start date
**FY09 to Date

Complaints Received*
FY 2001-2009**



***Includes All Branches**
****FY09 to Date**

CI Complaint-Related Inspection Assignments* CDER, FY 2001 – 2009**



***Based on Assignment Issued Date**
****FY09 to Date**

1/5/10

Rationale for Inspections

When Are Inspections Needed?

- For Cause (complaints from any source)
  - Substantiation of allegations that raise concerns regarding data integrity or the rights, welfare, and safety of study subjects have been compromised
- PDUFA-Related
  - All NMEs
    - Clinical Investigators
    - Sponsors
  - NDA/BLA Supplements
    - Inspections not always required
    - Significant expansion of the indication
    - Significant expansion of the patient population
    - Significant safety concern(s)
    - Data integrity issues

Specific Reasons For Inspections
(but not limited to…)

- Evidence/suspicion of the following
  - Misrepresented data
  - Unrealistic data
  - Rejection by the sponsor of investigator data
  - Under-reporting or delay in submission of adverse events
  - Inadequate monitoring of clinical investigations
  - Inadequate or inappropriate informed consent
  - Delayed or inappropriate IRB approval
  - Significant financial interest in the product by the investigator
  - Other potential concerns as they arise

Specific Reasons for Inspections (con't)

- Study not conducted under an IND
- Insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- a serious issue to resolve; e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

Selection of Sites to Audit

Rationale For Site Selection

- Site selection can be based on:
  - A specific safety concern at a particular site or sites
    - based on review of AEs, SAEs, deaths, or discontinuations
  - A specific efficacy concern based on review of site specific efficacy data
    - Efficacy differential between sites
    - Final outcome driven by a particular site or sites
    - Efficacy outcome different than expected based on mechanism of action of drug
  - Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results

Site Selection Considerations: Safety

- Evaluate Safety Data.
  - Are there sites with more frequently reported AEs, SAEs, Deaths?
  - Have more subjects discontinued from a particular site compared to others?
  - Are expected adverse effects for class of drug or particular drug not reported at a particular site/or sites?

Site Selection Considerations: Efficacy

- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?

Site Selection Considerations: Misconduct

- Are there concerns that the data may be fraudulent or inconsistent?
  - Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
  - Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations.
  - Are there a significant number of protocol violations reported at one or more particular sites?
  - Are the types of protocol violations suspicious for clinical trial misconduct?

Site Selection Considerations: Future Options

- Risk-based Site Selection Tool
- Purpose: Tool to assist in selection of clinical sites for inspection
- Sponsor asked to provide electronic submission of dataset with individual clinical investigation sites clearly identified, including characteristics and outcome of study at site level.
- Pilot currently ongoing in DAIOP, DSPTP, DAVP, DCRP

Inspection Processes

Inspection Schedule of Events

- DSI submits assignment to ORA based on review of
  - Complaints
  - Consults related to PDUFA work
- ORA conducts an inspection
  - FDA Form 483 may or may not be given
- ORA submits Establishment Inspection Report (EIR) to DSI
  - Inspection receives prelim. compliance classifications
- DSI reviews EIR
  - Provides inspection summary to review division for PDUFA
  - Provides final compliance classification
- DSI takes regulatory action if warranted
  - Submits a letter to the CI

DSI Inspection Consults

- For applications needing inspection(s), inform DSI ASAP
- Invite DSI staff to all meetings (to include pre-NDA and filing/planning)
- Discuss site selection with DSI if you have questions
- Send consult form ASAP, keeping Goal Dates in mind

DSI Does Not…

- Directly participate in all inspections

- Have complete control of the timing of inspections
  - Foreign Inspection Scheduling Issues
    - Travel visas
    - Notices of Foreign Travel (NFTs)
    - Coordination with sites to be inspected

  - ORA Field Investigators prioritize work based on workload
    - Food related issues, such as outbreaks associated with Fresh Spinach or Melamine in Pet food may take precedence

Generation of Assignments

Assignments

- DSI Reviewers generate Field Assignments for clinical investigators and submit them to ORA
- Assignment Content
  - Description of the investigational drug, proposed indication, and known safety profile of drug or class of drug, if drug is NME
  - Description of disease
  - Description of each protocol to be audited
  - Rationale for Site Selection
  - General and Specific Instructions
  - Background Materials

Background Materials

- Protocol/Amendments
- Sample Case Report Form
- Data Listings
  - primary efficacy endpoint(s)
  - key secondary efficacy endpoint where applicable
  - adverse events, serious adverse events, and deaths
  - protocol deviations
  - subject randomization
  - subject discontinuations
  - concomitant medications

Clinical Investigator Inspections: What do we look for during the inspection?

The FDA Inspection (Audit) compares

- Source Document Medical Record Data

  vs

- Case Report Forms

  vs

- Data Listing Submitted to NDA

Verify

- Source of subjects; Did subjects exist?
- Did they have the disease under study?
- Did they meet inclusion/exclusion criteria?
- IRB Review Obtained? Consent obtained?
- Adherence to protocol?
- Verify primary efficacy measure
- Adverse events?
- Safety data: Labs, EKG etc.
- Drug Accountability? Blinding of data?

What is Generated by the Field After an Inspection

Form FDA 483: Inspectional Observations

- Left with CI at close of inspection
- Immediately available via FOI

Establishment Inspection Report (EIR)

- Prepared by field investigator after inspection
- Includes exhibits supporting observed deficiencies

DSI Review of Inspection Results

- DSI reviewers review the EIR, FDA Form 483 and all exhibits
  - Evaluate the clinical relevance of findings
  - Evaluate validity of findings
- For NDAs/BLAs, a Clinical Inspection Summary is generated providing salient information from inspection to the Review Division, once ALL EIRS are submitted
- Letters are generated for submission to Clinical Investigators
  - OAI, VAI, VAI-R, or NAI

Role of Inspection Results

- Aid DSI/Review Divisions in determining approvability of a marketing application
  - Assurance that safety and efficacy data are valid
- Public Health Impact
  - Regulatory Action by FDA/DSI
    - Warning Letters
    - NIDPOE
    - Disqualification of CI
  - Criminal Investigation by OCI

Compliance Classifications

NAI No Action Indicated

- Firm is in compliance; Data Acceptable

VAI Voluntary Action Indicated

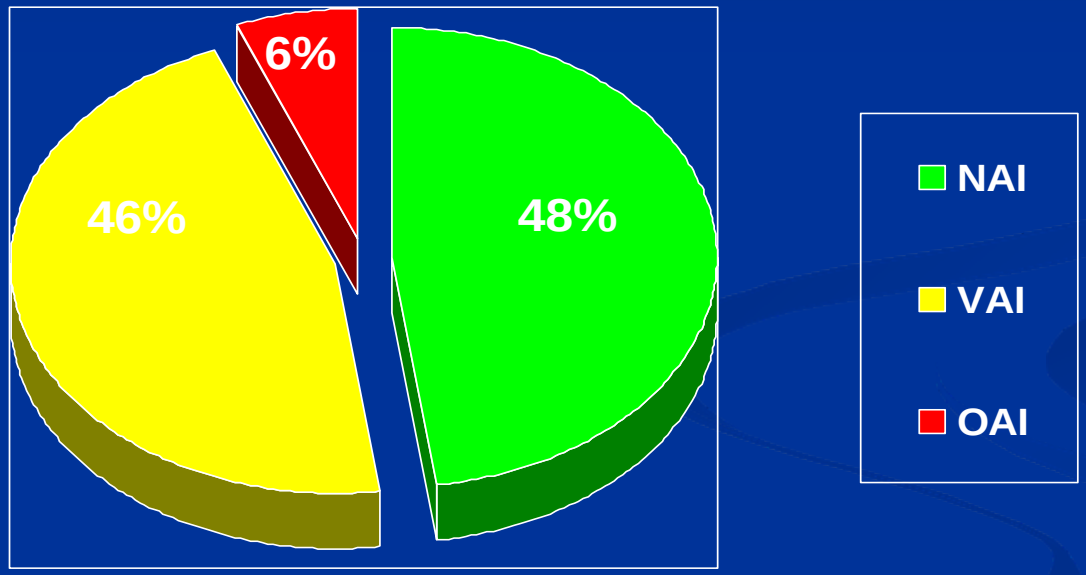
- Deviations from the regulations
- Voluntary correction requested; data or portions thereof may/may not appear acceptable
- Reference:

21 CFR part 50 & 312; Clinical Investigators
21 CFR 312.60; 312.61; 312.62; 312.64; 312.66; 312.68; 312.69

OAI Official Action Indicated

- Serious non-compliance requiring regulatory or administrative action by FDA
- Data Unacceptable
- Reference: 21 CFR 312.70 (Disqualification of CI)

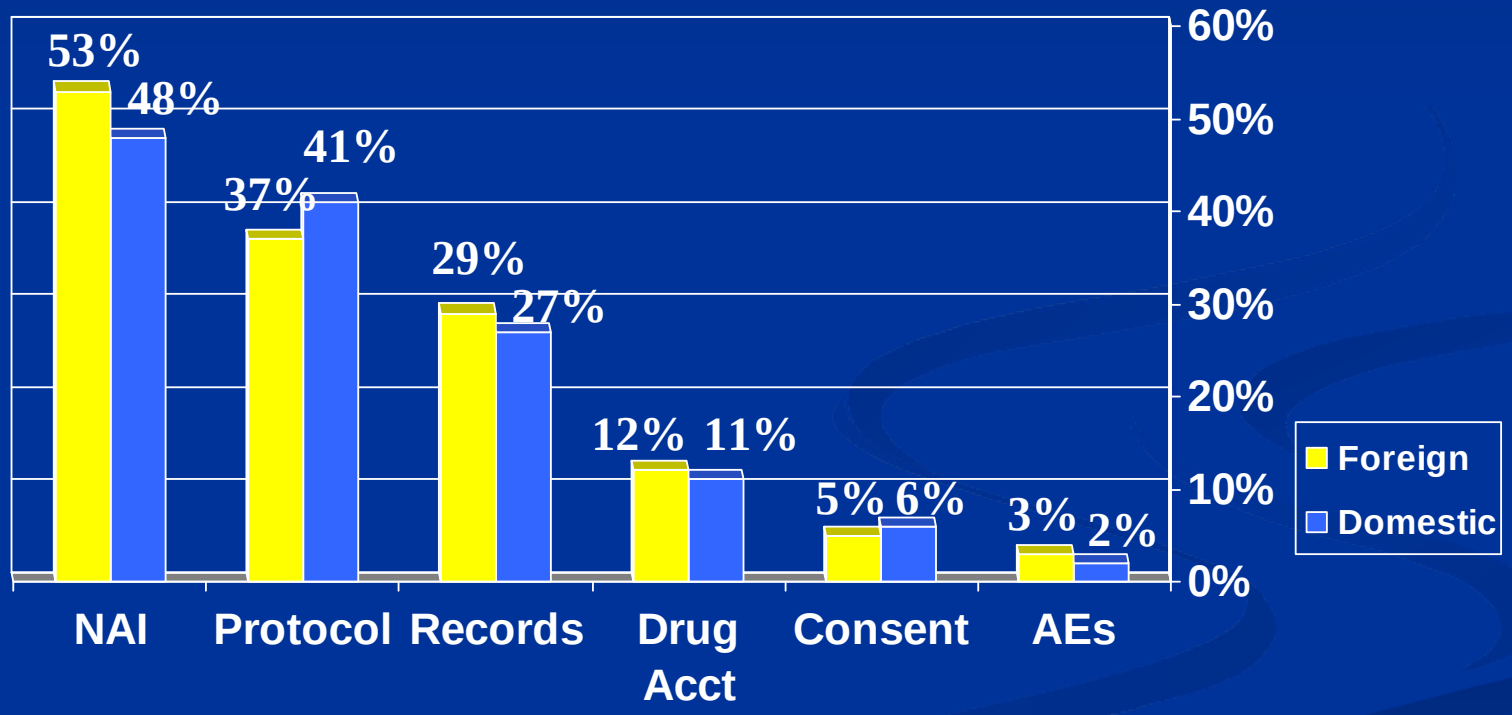
Clinical Investigator Inspections Final Classification* FY 2009**



Total inspections with final classification = 624
Includes OAI Untitled Letters

***Based on Letter Issued Date**
****FY09 to Date**

Clinical Investigator Deficiencies CDER Inspections - FY 2009**



Foreign n = 120*
Domestic n = 401*

***Based on Letter Issued Date**
****FY09 to Date**

Examples of Violative Findings

Violative Actions

- revise the protocol without obtaining the sponsor's written concurrence
- neglect to submit the revised protocol to IRB for approval
- forget to obtain written informed consent and provide oral explanation of the study
- forget to update consent forms to reflect changes in the protocol

Violative Actions

- over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- erase, white-out or obliterate original data entry either in CRFs or medical charts
- accept suggested changes to study data without checking the source documents or without justification for such changes

Violative Actions

- backdate the consent forms and signatures
- forget to obtain IRB approval of consent form revisions
- permit changes to study data without the investigator's concurrence, especially after the investigator has "signed-off" the completed CRF
- blame anyone for inaccuracies in the CRFs

Violative Actions

- create fake records or patients by using demographic data or using blood, urine and tissue samples from other subjects
- alter patients' diaries to reflect a positive outcome
- use your staff as subjects in a study not having the condition(s) under investigation
- destroy study records

DSI Home Page

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm

Information Sources

DSI
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm

List of Disqualified or Restricted Investigators
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

Warning Letters
http://www.fda.gov/foi/warning.htm

NIDPOE Letters
http://www.fda.gov/foi/nidpoe/default.html

Debarment List
http://www.fda.gov/ora/compliance_ref/debar/default.htm

Clinical Investigator Inspection List
http://cdsml2/dsi/cliil/